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DOI: https://doi.org/10.1097/PAF.0000000000000265

Papilledema as a Diagnostic Sign of Cerebral Edema on Postmortem Magnetic Resonance Imaging

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Abstract: The purpose of this study was to investigate papilledema (PA) as a diagnostic criterion for the presence of antemortem or agonal cerebral edema despite normal postmortem brain swelling on postmortem magnetic resonance imaging (PMMR) in comparison with conventional autopsy.

One hundred subjects with head PMMR and autopsy were included in this study. The sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), and accuracies were calculated in terms of the PA, PMMR, and cerebral edema on autopsy. Spearman *r* tests were used to analyze the linear correlations of PA and the radiological and autoptic determination of cerebral edema.

In autopsy, the sensitivity regarding the presence of PA and cerebral edema was 66.2% (PPV, 70.5%), and specificity was 48.6% (NPV, 28.3%), with an overall accuracy of 60%. On PMMR, the sensitivity was 86.6% (PPV, 95%). The specificity was 90.9% (NPV, 34%), with an overall accuracy of 88%. The Spearman correlation revealed a statistically significant result ($P < 0.001$), which indicated a strong linear correlation of the presence of PA and cerebral edema with the autopsy results and the PMMR results.

The presence of PA may aid in the diagnoses of cerebral edema despite normal postmortem brain swelling based on PMMR.

Key Words: Virtopsy, papilledema, postmortem radiology, PMMR, cerebral edema, autopsy

(*Am J Forensic Med Pathol* 2016;00: 00–00)

Postmortem imaging (Virtopsy) is currently an established tool for enhanced forensic investigations of the deceased.[1–4] Postmortem computed tomography (PMCT) is paramount for state-of-the-art examinations in forensic settings due to its wide availability and rapidity.[5,6] Postmortem computed tomography is an established method, particularly for the detection of fractures, gas-containing structures, and foreign bodies and radiological identification.[7–13]

In contrast, postmortem magnetic resonance imaging (PMMR) is not at the disposal of a multitude of forensic centers. However, PMMR offers far better soft tissue contrast than PMCT and therefore acts as a method that is complementary to PMCT, particularly for cases of, for example, cardiac death and cerebral pathology.[14–18]

Swelling of the brain is a typical and normal finding on postmortem images and may incorrectly elicit interpretations of antemortem agonal cerebral edema as pathological.[4,19–22] Therefore, the detection of antemortem or agonal cerebral edema despite normal postmortem alterations, such as brain swelling, remains difficult based on imaging, fairly subjective, and based on the reader's experience.[19]

Berger et al[19] evaluated several cerebral features related to the reliable detection of cerebral edema and stated that, as diagnostic criteria on PMCT, first, the narrowing of the temporal horns and, second, the bilateral herniation of the cerebellar tonsils despite Hounsfield unit changes in terms of the ratio of gray and white matter are diagnostic criteria.

Papilledema (PA) is an optic disk swelling that is a secondary clinical sign of increased intracranial pressure and is therefore a potential criterion for cerebral edema.[23–27] Papilledema is nearly always a bilateral pathology and usually appears in cases with elevated intracranial pressure due to the transmission of the cerebrospinal fluid to the optic nerve sheath.[23,25,26,28,29] In addition to cerebral edema, there are other medical conditions that may lead to PA, such as pseudotumor cerebri, decreased or increased cerebrospinal fluid resorption, space-occupying intracranial lesions, and even certain drugs.[26,28,29] Papilledema is well defined on PMMR because of its excellent soft tissue contrast and the lack of disturbing motion artifacts of the eyes; in addition, PA is also visible to a lesser degree on PMCT.

The purpose of this study was to investigate PA as a diagnostic criterion for the presence of antemortem or agonal cerebral edema despite normal postmortem brain swelling on PMMR in comparison with conventional autopsy.

MATERIALS AND METHODS

Study collective

One hundred subjects who underwent head PMMR and conventional autopsy for a 26-month period (from the end of 2012 to the beginning of 2015) were included in this study. Cases with destruction of the head, progressed putrefaction, thermal impacts, and bulbar lesions (ie, shrinkage, globe rupture, posttraumatic lesions, prosthesis of the bulb, and retinal hemorrhage) and PMMRs of neonates were excluded. No cases with PA associated with tumorous or obstructive pathologies (eg, pseudotumor cerebri) or normal pressure hydrocephalus were included in the retrospective evaluation.

In all cases, the legal authorities mandated full forensic autopsies. The responsible local justice department approved this study. The subjects' ages ranged from 0.2 to 93 years (mean, 46.2 years) and included 40 women and 60 men. The interval between death and PMMR was at least 1 hour, the maximum was 228 hours (mean, 29.5 hours), and the death-to-autopsy intervals ranged from 7 to 231 hours (mean, 39.7 hours).

The causes of death were predominantly central regulatory failure (n = 59) followed by asphyxia (n = 24), cardiac arrest (n = 14), strangulation (n = 2), and drowning (n = 1; Figs. 1, 2). The predominant manner of death was suicide (n = 32) followed by natural death (n = 27), accident (n = 24), and homicide (n = 14). Unclear manners of death in terms of accident versus suicide (n = 2) and homicide versus suicide (n = 1) were noted.

Manuscript received May 24, 2016; accepted June 24, 2016.
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ISSN: 0195-7910/16/0000–0000
DOI: 10.1097/PAF.0000000000000265

Cause of Death	Manner of Death	N=100	
Central regulatory failure	Suicide	15	59
	Natural	16	
	Accident	18	
	Homicide	8	
	Accident vs suicide	2	
Cardiac arrest	Suicide	1	14
	Natural	11	
	Accident	1	
	Homicide	1	
Asphyxia	Suicide	15	24
	Accident	5	
	Homicide	4	
Strangulation	Suicide	1	2
	Homicide	1	
Drowning	Homicide vs suicide	1	1

FIGURE 1. A comprehensive overview of the causes and manners of death of the study sample.

Autopsy

The conventional autopsies included dissections of the 3 body cavities (skull, thorax, and abdomen) and were performed in each evaluated case. The determinations of cerebral edema were based on the total brain weight (age dependent), the consistency of the brain parenchyma (reduced in edema), and the inspections of the morphologies (flattening of the gyri and indentation of the cerebellar tonsils) in consensus with the subjective assessments of the forensic pathologist.[19,30] Histology was not consistently performed. Toxicology was performed when mandated by the legal authorities and in suspected cases of drug abuse and intoxication.

PMMR Image Acquisition

Postmortem magnetic resonance imaging was performed using a 3.0-T MR unit (Achieva TX; Philips, Best, The Netherlands) after each case that was delivered to the morgue was scanned by PMCT. Each evaluated case underwent a standard head protocol using an 8-element phased-array coil that included T1- and T2-weighted sequences (4 mm), as well as fluid-attenuated inversion recovery, venous blood oxygenation level-dependent, and diffusion-weighted imaging sequences. The PMMR image evaluations for PA were limited to the T2-weighted turbo spin echo sequence using the following parameters: slice thickness, 4 mm (children, 2 mm); acquisition voxel size, $0.57 \times 0.72 \times 4$ mm; repetition time, 3000 ms; and echo time, 80 ms.

PMMR Data Analysis

The image evaluations included visual assessments of antemortem or agonal cerebral edema based on the criteria of Berger et al,[19] the presence of optic disc swelling (PA), buckling of the optic nerve, the presence of perioptic nerve fluid, and measurements of the discs and nerve diameters on both sides on magnified and standard axial slices collected with the T2-weighted sequence. The image evaluations were performed with a multimodal reading solution (Syngo.via, version VA30A; Siemens, Medical Solutions, Erlangen, Germany). A board-certified radiologist with experience in postmortem forensic imaging performed the data analysis while blinded to the actual autopsy findings.

Statistical Analysis

The statistical analyses were performed using the commercial statistical software package SPSS (release 20.0; IBM, Chicago, Ill) and the open-source statistics software SOFA (version 1.4.5; Statistics Open For All, Paton-Simpson & Associates Ltd, Auckland, New Zealand).

The sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), and accuracies were calculated in terms of the PA, PMMR, and cerebral edema on autopsy.

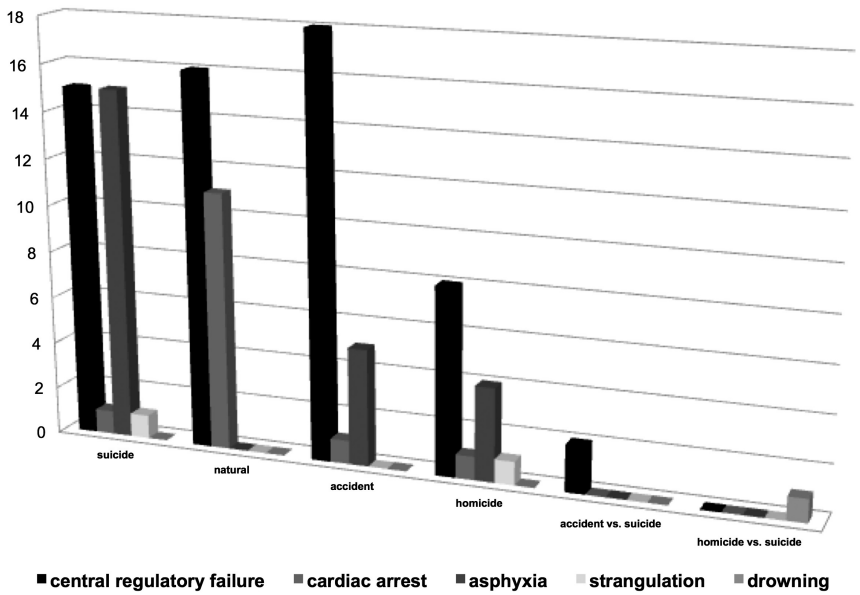

FIGURE 2. Diagram displaying the causes and manners of death of the study population that indicate that most cases died because of central regulatory failure after accidents (n = 18). The most common overall manner of death was suicide.

		Autopsy Cerebral Edema	
		+	-
PA	+	43 (66.2%)	18 (51.4%)
	-	22 (33.8%)	17 (48.6%)

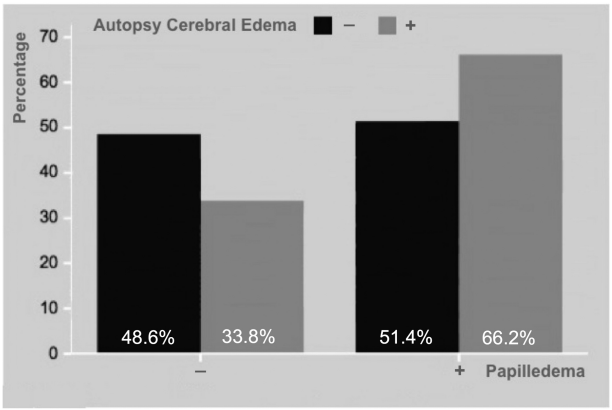

FIGURE 3. Diagram illustrating the distribution of the cases in terms of PA and cerebral edema as detected on autopsy (blue, negative; gray, positive) with graphic and tabular displays of the sensitivity (66.2%), the false-positive rate (51.4%), the specificity (48.6%), and the false-negative rate (33.8%).

Tests for normality (for PA, PMMR, and cerebral edema on autopsy) were not strictly normal. Therefore, Spearman *r* tests ($P < 0.001$) were used to analyze the linear correlations of PA, the radiological findings of cerebral edema, and the determinations of cerebral edema on autopsy.

RESULTS

Autopsy

On the basis of the previously mentioned criteria, 65 cases presented with cerebral edema, and 35 presented without pathology. The true positive (sensitivity) rate regarding the presence of PA and cerebral edema was 66.2%, and the false-positive rate was 51.4%, with a PPV of 70.5% (Fig. 3). The specificity was 48.6%, with a false-negative rate of 33.8% and an NPV of 28.3% (Fig. 3). The overall accuracy was 60%, with a positive likelihood ratio of 1.3, which indicates that the test discriminated correctly, and the negative likelihood ratio was less than 1 (0.7). The diagnostic odds ratio was 1.8.

The Spearman correlation revealed a statistically significant result ($P < 0.001$), which indicated a strong linear correlation of the presence of PA and cerebral edema with the autopsy results. In addition, the linear correlation between the presence of detected cerebral edema during autopsy and on PMMR was significant ($P < 0.001$).

However, there was no correlation between the buckling of the optic nerve and the detection of edema during autopsy. The postmortem interval (ie, the death-to-autopsy time) was not correlated with PA.

PMMR Data Analysis

On the basis of visual inspections according to the methods of Berger et al,[19] 67 subjects were positive for the presence of cerebral edema, and 33 were not. The true positive rate (sensitivity) regarding PA was 86.6%, the false-positive rate was 9.1%, and the PPV was 95% (Fig. 4). The specificity was 90.9%, the false-negative rate was 13.4%, and the NPV was 34% (Fig. 3). The overall accuracy was 88%, with a positive likelihood ratio of 9.5 and a negative likelihood ratio of 6.8. The diagnostic odds ratio was 1.4.

The Spearman correlation was statistically significant ($P < 0.001$) and indicated a very strong linear correlation of the presence of PA and cerebral edema on PMMR results.

Buckling of the nerve and PA exhibited a significant linear correlation with the detection of edema on PMMR ($P < 0.001$). The nerve and disc diameters exhibited no influence on PA or correlation with brain edema. The postmortem interval (ie, the time from death to the PMMR scan) was not correlated with PA.

Manner and Cause of Death

Regarding the cause of death, there was no significant correlation with PA ($P = 0.06$). However, there were tendencies for the presence of PA to be related to asphyxia and central regulatory failure. Moreover, there were strong correlations between PA and the manner of death ($P < 0.001$, Spearman test); PA was more likely to be present in cases of natural death than accidents, and the highest correlations were observed for accident versus suicide and homicide versus suicide. The absence of PA was more likely to be observed in cases of suicide and especially homicide. The presences of buckling of the nerve, PA, and edema on PMMR were significantly linearly correlated ($P < 0.001$).

DISCUSSION

The present research demonstrated that there was a discrepancy regarding the evaluation of PA based on autopsy results in terms of the presence of cerebral antemortem/agonal edema and the evaluation of the presence of edema based on PMMR. Regarding PA, the sensitivity was moderate, and the specificity was fair, which led to a mediocre accuracy compared with the evaluation of

		PMMR Cerebral Edema	
		+	-
PA	+	58 (86.6%)	3 (9.1%)
	-	9 (13.4%)	30 (90.9%)

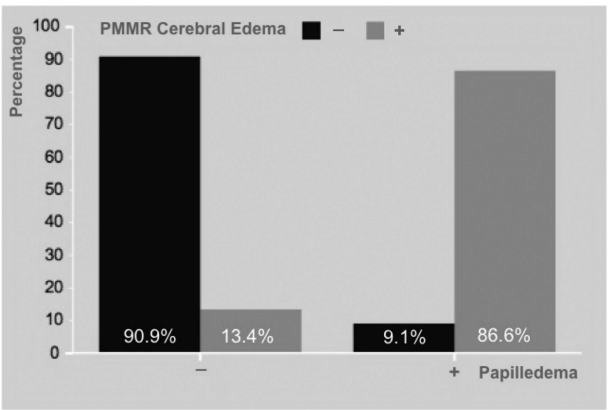

FIGURE 4. Diagram illustrating the distribution of the cases in terms of PA and cerebral edema as detected on PMMR (blue, negative; gray, positive) with graphic and tabular displays of the sensitivity (86.6%), the false-positive rate (9.1%), the specificity (90.9%), and the false-negative rate (13.4%).

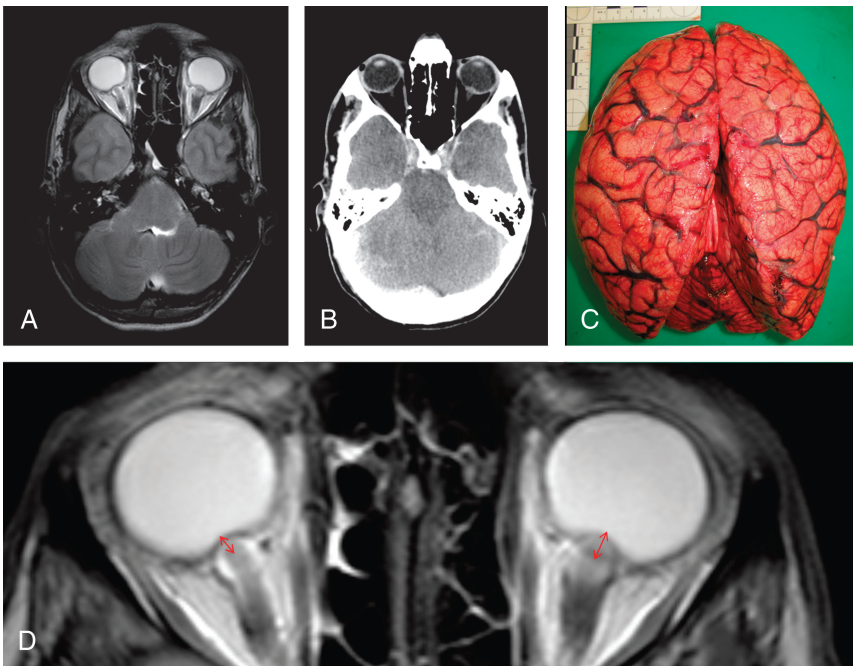

FIGURE 5. This case exhibits extensive brain edema as detected on PMMR and autopsy. The brain weight was 1540 g for this 27-year-old man who died of central regulatory failure due to a ruptured cerebral aneurysm. A, T2-weighted PMMR sequence showing the extensive PA. B, Postmortem computed tomography for comparison with A. Note the hypodense cerebral tissue with the loss of the white and gray matter differentiation as well as the PA, which is not as distinct as it is on PMMR (A). C, Autopsy photograph of the brain showing flattened gyri and sulci and a soft consistency of the brain that is indicative of cerebral edema. D, Magnified view of the PA (indicated by the red arrows) shown in A with clear edemas located at the papillae of both eyes. Note the fluid along the optic nerve sheath.

the presence of cerebral edema on autopsy. The false-positive rate was high at slightly more than 50%. In contrast, PA exhibited a high sensitivity, a low false-positive rate (<10%), and an excellent PPV regarding the presence of cerebral edema according to PMMR evaluations (Figs. 5, 6). Accordingly, the specificity and accuracy were very high. Moreover, the positive likelihood ratio of 9.5 indicated that this test was very useful.

These results lead to several conclusions. First, the selected gold standard should be discussed. Autopsy was established as the gold standard. However, autopsies are strongly observer dependent and are not prone to reevaluations.[12] The criteria for brain edema are the weight of the brain (the assessment of which should be age dependent) and the consistency and appearance of the morphology (in terms of the sulci, gyri, and tonsils).[31,32] However, the subjective interpretation is also strongly dependent to the observer's experience and empirical knowledge. In contrast, imaging results, PMMR results in the case of this study, are infinitely available for reevaluation by additional experts. Berger et al[19] evaluated specific imaging criteria for the postmortem assessment of antemortem/agonal edema and stated that 2 diagnostic criteria are relevant (ie, the delineation of the temporal horns and the symmetric herniation of the cerebral tonsils) as measurable parameters for the detection of cerebral edema on imaging. In clinical practice, imaging is considered the gold standard for the assessments of brain morphology and exhibits a strong correlation with the findings of decompressive brain surgery.[33–36] Hence, consideration should be given to the selection of a future gold standard regarding the evaluation of cerebral edema during autopsy and should favor the critical evaluation of data obtained from forensic brain imaging.[37]

Another hypothesis regarding the presence of PA could be related to a postmortem increase in fluid accumulation within the optic nerve sheath and subsequent increased swelling of the papilla. However, in this situation, increased fluid within the nerve sheath would be in direct correspondence with the brain due to the subarachnoid space and would certainly be increased in brain edema despite the typical swelling of the postmortem brain. Therefore, the assessment of PA can be considered as a diagnostic indicator for the assessment of cerebral edema on PMMR and may aid the differentiation of postmortem swelling of the brain and true cerebral edema. Buckling of the optic nerve may serve as a further indicator of PA, but this factor should be taken into account with care because there may also be an anatomical variation.

The postmortem interval had no influence on the outcome of this study. However, no putrefied subjects were included in the study. The correlation of the absence of PA in homicides and suicides probably resulted from these deaths being more abrupt than the natural deaths and accidents (the latter patients may have survived in the hospital for some time before death). The natural deaths and accidents may have allowed more time for the development of cerebral antemortem and/or agonal edema compared with the cases in which death was sudden due to homicide or suicide. The 3 cases in which the manner of death was unclear in terms of accident versus suicide and homicide versus suicide comprised a small study population and may have also been part of the natural death and accident group that was more likely to present with PA.

Clearly, there are certain limitations to this study, such as the chosen imaging modality and its current low level of availability in morgues. In the future, this limitation may be overcome by increased availability of PMMR scanners for forensic purposes worldwide. In addition, the slice thickness was too thick for the assessment of the PA statuses of the neonates, but this issue could be improved by creating a specific and short protocol over the bulb

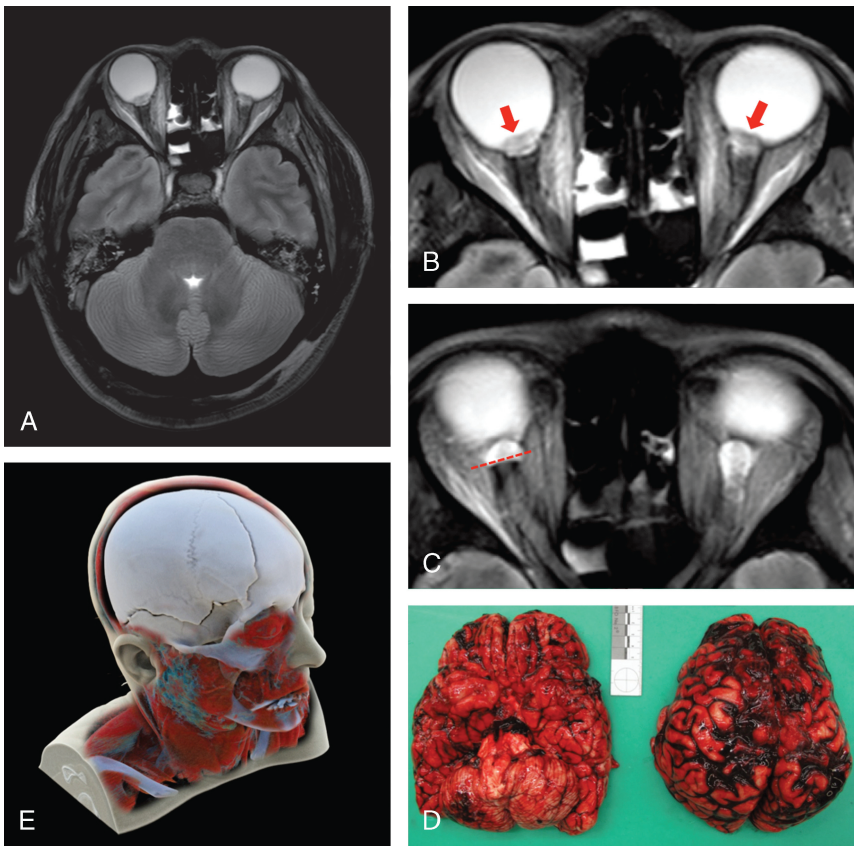

FIGURE 6. This case died because of a bicycle-tramway collision. The accident led to extensive skull fractures with concomitant subarachnoid hemorrhaging (SAH). The 45-year-old woman survived for a short interval in the intensive care unit before death. A, T2-weighted PMMR sequence showing the bilateral PA. B, Magnified view of the bulbs. The red arrows depict the considerable swelling of the optic discs. The right bulb exhibits a longitudinal configuration that most likely indicates myopia in this eye. C, Magnified view of the eye bulbs. This adjacent PMMR slice illustrates a typical postmortem sedimentation effect of the corpuscular particles of the blood within the optic nerve sheath on the right (red dotted line) and fluid accumulation along both optic nerves that illustrates the direct communication between the nerve sheath and the brain via the subarachnoid space because this case presented with SAH. D, Autopsy photograph displaying the brain swelling and the extensive SAH due to head trauma. The brain weight was 1590 g. E, Three-dimensional volume rendering of the skull as viewed from the anterior right. Note the severe skull fractures on the right.

with fewer but thinner slices (<1.5 mm). This protocol would also eliminate potential false measurements due to partial volume effects. Progressed putrefaction, mummification, and thermal influences lead to changes in the eye bulb (eg, gas accumulation, bulb shrinkage, and dehydration) that could act as further limitations.[4,20,38,39] Aged subjects tend to accumulate more fluid along the optic nerve sheath, and the amount of optic nerve subarachnoid fluid is variable and may be substantial even in healthy adults. This variability has to be taken into consideration when assessing the optic nerve and its sheath.[40] In the future, research regarding the assessment of PA and cerebral edema on PMCT in larger cohorts would be desirable.

However, the detection of cerebral edema despite postmortem changes may be successful because the presence of PA may aid diagnoses based on PMMR.

ACKNOWLEDGMENT

The authors express their gratitude to Emma Louise Kessler, MD for her generous donation to the Zurich Institute of Forensic Medicine, University of Zurich, Switzerland.

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